EXPERIMENTAL CONTROLS IN CLINICAL DERMATOLOGIC INVESTIGATION*

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Investigation of the comparative effectiveness of different methods of treatment of a particular disease of the skin is often a difficult undertaking. We have become very conscious of the numerous possible sources of error in the pursuance of adequate clinical dermatologic investigations in our own clinics, and keenly appreciative of the deficiencies of certain of our studies in the past. It is proposed in this report (a) to list certain specific difficulties which have arisen in the course of such experiments, (b) to cite examples of some widely accepted methods of treatment, the value of which has apparently never been determined conclusively by planned experiments, and (c) to summarize briefly and criticize three illustrative clinical investigations from this department.

Much has been said and written concerning the necessity for increased facilities for basic studies of the normal and disturbed physiology of the human skin. It is probable that the skin is the most neglected organ of the human body in terms of lack of support of fundamental studies of it. In connection with this deserved emphasis upon the need for basic laboratory studies, it is perhaps not amiss to point out a similar pressing need for planned clinical investigations, and to emphasize that adequate clinical studies are often much more difficult to carry to a conclusion than are many laboratory studies.

In a laboratory study in which animals are used, the subjects may ordinarily be kept under conditions of excellent control, and such studies, if well planned, usually offer one or more accurate means of measuring the results obtained. On the other hand, in studies of the treatment of disease in man, controlled conditions of treatment of the subject, and accurate standards of measurement of the results may be exceedingly difficult to attain. Since the results of studies dealing with the treatment of disease in man are more likely to find immediate application by other physicians than are studies in animals, however, it is obvious that the responsibility of the clinical investigator to plan his studies logically and carry them out conclusively is fully as great as that of the laboratory scientist. Published reports of new methods of treatment are ordinarily merely a record of observations.

The difference between observation and experimentation may be sharply drawn, but usually is not. An observation records a fact, a series of facts, a sequence of events, a result. The result may be due to the passage of time, to a method of therapy, to psychosomatic influences, or to some other factor in which the investigator might be interested. The observation may or may not indicate the *cause* of the result, which may include several factors.

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Albritton (1) has strikingly and ingeniously summarized the various factors which may produce a result, in Fig. 1. Reading of Albritton's monograph is a stimulating experience, and analysis of reports of clinical experiments from one's own department on the basis of his simply stated criteria is most revealing. It will be found disturbingly apparent in the case of some clinical reports, that the design of the experiment made a final conclusion impossible; in others, the presence of uncontrollable "associated agents" made the conclusions equivocal; while, in all too few, the conclusions were valid.

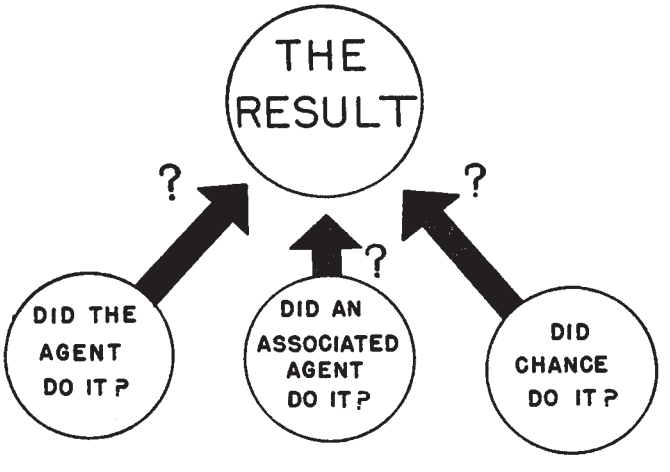

FIG. 1. Possible causes of a result

The following are the chief requirements of a planned study designed to provide data from which conclusions may be drawn:

1. Problem: something to be evaluated
2. Standard apparatus to be used in the evaluation
3. Standard procedures to be used throughout the experiment
4. Standard interpretation of results
5. A standard against which to measure results (control)

Investigations of methods of treatment of diseases of the skin offer difficulties common to any experimental study, and must be planned carefully if unproductive work and expense are to be avoided, and if the conclusions reached are to be valid. The skin offers certain advantages for study in that it is easily observed. In other respects, however, it offers formidable barriers to the performance of controlled clinical experiments. Some of the difficulties which have been encountered in our own clinics are as follows:

(1) *The difficulty of standardization of "associated agents".* The human skin is exposed to a wider variety of agents than any other organ of the body. In addition to almost innumerable contactants having primary irritant or sensitizing capacities, the skin is subjected to constantly changing thermal and actinic influences, and to a variable subcutaneous bath of highly complex nature. These factors are

only partially controllable. The profound influence of environmental and other factors is well stated by Sulzberger and Wolfe (2), as follows, "environmental change and hospitalization exercise such remarkable beneficial effects that in many dermatoses this change is one of the most effective of dermatologic weapons." Our experience is in complete accord with this, and has led us to exercise great caution in evaluating the result of almost any type of treatment for skin diseases of unpredictable course, in patients who have just been removed from their home environment to a hospital.

(2) *Difficulties in the standardization of measurements.* Hopkins (3) has recently discussed this problem. If a lesion of the skin disappears completely, the immediate result, whatever the cause, is obvious. In many diseases, however, the extent of partial improvement of the lesions is difficult to measure, and a wide variation in the "percentage of improvement" may be estimated on the same patient by different observers. In determining changes in subjective symptoms, particularly itching, the measurement is subject to great inaccuracies.

(3) *Lack of accurate knowledge of the normal course of the disease under treatment.* It is obviously impossible to determine the effectiveness of a particular method of treatment unless something is known of the course of the disease without treatment, or under placebo therapy, is known. In the case of some diseases, e.g., psoriasis and lupus vulgaris, it is known that few patients recover. In other diseases, e.g., atopic dermatitis, the course of the disease is extraordinarily erratic, and collection of a "control" series of sufficient size to determine the effects of associated agents and of chance, is extremely difficult. Even in the case of diseases presumed to have a well-established simple cause, e.g., impetigo or scabies, great variations in symptoms, severity, and extent may be noted. Acne, an almost physiologic condition, disappears in most individuals, but in what percentage of them, and at what ages, is not definitely known.

(4) *The enthusiasm of the individual investigator.* Examples of this as a source of error in clinical investigations are numerous. Without the quality of enthusiasm in the investigator, no data will be accumulated; with misdirection of it, the plan of the experiment may be disregarded, the measurements made in error, and the data misinterpreted. If an investigator becomes prematurely convinced of the value of the method of treatment under study, random sampling of his clinical material becomes increasingly onerous and distasteful, because his every impulse as a good physician is against the denial to any patient of a method of treatment which he believes to be effective. In addition, his enthusiasm may act as an extraordinarily effective method of psychotherapy.

(5) *Lack of adequate clinical material.* The importance of this factor is obvious, but we have several times fallen into the discouraging error of attempting a planned clinical investigation without sufficient prospect of collecting enough data to permit conclusions. Under very unusual conditions, study of a single patient may permit conclusions as to the value of a particular method of treatment, but this is rare.

(6) *Certain corollary factors.* (a) Lack of support. Few departments of dermatology have anything approaching adequate support for planned clinical experi-

ments. It has been our experience that clinical investigations undertaken simply as a part of a routine clinic or office practice, without provision for assignment of special facilities and personnel, rarely adhere to plan. In any study involving more than a few patients, it has been our policy not to undertake it unless the facilities are the equivalent of one full-time person assigned to the project, and it is believed that grantors would be well-advised to think of support of serious clinical investigation in such terms.

(b) Pressure from grantors. One of the most exquisite forms of torture for scientists is the habit of some granting agencies, government, foundational, and pharmaceutical alike, to make specific grants for investigational projects for a term of one year, with continuance of the grant dependent upon the prompt elaboration of significant data, and with too frequently an unwritten provision that such data must permit positive conclusions as to the effectiveness of a particular method of treatment. This has been a source of erroneous conclusions and premature publication.

The above list is incomplete and in many respects superficial in its approach. Reference is again made to more extended and fundamental expositions of the requirements of a properly designed experiment and the judgment of evidence obtained therefrom.

In spite of the difficulties of planned experiments in dermatology, as outlined above, numerous papers of value are steadily appearing, and one is impressed with the genuine progress which has been made in clinical investigation in this field during the recent years. However, many examples may be cited of methods of treatment which have no apparent sound foundation, and which may have potentialities for harm, e.g., the following.

(1) *Treatment of chronic discoid lupus erythematosus.* Since the basic etiology of this disease is poorly understood, it is not surprising that no adequate method of treatment has been devised, with the possible exception of ACTH and Cortisone. It is well-established that some types of therapy are frequently harmful, e.g., ultra-violet rays, but other methods of treatment are frequently used, have demonstrable potentialities for harm, and are subjects of dispute as to efficacy. These include injection of gold salts, of bismuth, and of arsenicals. There has apparently been no planned study of the treatment of this disease.

(2) Other methods of treatment which have been in common use for years, concerning which there are no reports based on planned experiments from which conclusions may be drawn, include: (a) autohemotherapy in the treatment of dermatitis presumed to have an allergic basis, or of psoriasis, (b) calcium salts by injection or by mouth. These are non-toxic methods of treatment, and probably have significant psychotherapeutic effects. There are, however, no data to indicate conclusively that either of them by themselves may be the *cause* of improvement of the eruption under treatment.

(3) *The treatment of acne.* Mention has previously been made of the profound influence of the associated agent of time in judging the effectiveness of any particular method of treatment of this disease. Bloch (4) has collected accurate and detailed information as to the incidence of acne, the time of onset, and the differ-

ence in incidence and severity between the sexes. There is, however, no comparable accurate information as to the time of spontaneous involution of acne, and the percentage of cases in which it occurs. It is quite probable that no such data will ever be collected. Nevertheless, it seems worth while to point out that many methods of treatment have been advised, and an attempt at evaluation made, without consideration of the associated agent of passage of time. With methods of treatment capable of producing serious side effects, such as x-ray therapy, the administration of arsenic, or injection of hormones, it is essential that data based on planned experiments be available. In the case of x-ray therapy, a study was carried out some years ago in which only one side of the face of patients with acne received x-ray therapy (5), and in relatively small series of patients treated, no significant difference in the progress of the acne on each side of the face could be detected in 19 of the 40 patients treated. Such a study might profitably be extended.

(4) *The treatment of warts.* Ordinary warts present an outstanding example of a disease of the skin due to a specific agent, a virus, in which psychotherapy has been demonstrated to have a profound effect. (6) It is obvious, therefore, that in the study of any particular method of treatment of warts, the associated agent of psychogenic influence is always operative to a greater or less degree. The subject of the treatment of warts has been the subject of a large number of papers in the medical literature, and among them very few in which the possible effects of agents other than treatment used have been considered.

As an example of the extent to which the requirements of a planned study have been observed or disregarded in the treatment of warts, a leading specialty journal (The Archives of Dermatology and Syphilology) has been reviewed for the period 1920 to 1948, and all reports dealing with the treatment of verrucae abstracted and subjected to analysis. It must be kept in mind that many of these papers were simply a report of a sequence of events, and the authors did not intend that sweeping conclusions should be drawn therefrom.

During this period of 28 years, 21 papers on the treatment of warts were published in the journal reviewed. The treatment of 2505 patients with warts was recorded in 16 of the papers, in five reports the number of patients treated was not stated. The reports appeared rather evenly over the 28-year period, indicating a steady sustained interest in the problem, and inferring the absence of any completely satisfactory method of treatment. In only two reports was the method of treatment compared in effectiveness with a control series of untreated patients or in a group receiving placebo therapy. In only one paper was the number of "controls" adequate. It is of interest that in both the papers where controls were included, as good or better results were obtained with placebo therapy as with the particular medication under study. In one study, "100%" cures of warts were reported as a "result" of intramuscular injections of bismuth subsalicylate. In another paper published 7 years later, 50% cures were reported after treatment with bismuth subsalicylate, but a cure resulted in 75% of patients with intramuscular injections of saline solution. Several papers reporting cures of warts in almost 100% of cases by the injection of sulfarsphenamine preceded publication

of the excellent paper by Allington (7) in which 52% of 105 patients with warts were cured by injections of sulfarsphenamine, and 48% of 120 patients by injections of colored saline solution. This is one of the best examples of a planned clinical study in the dermatologic medical literature.

A similar pattern of initial enthusiasm toward a particular method of treatment is seen in the treatment of verrucae by the method of injection of an autolysate of verrucous material. In the initial report of this method of treatment, 84% of the patients are recorded as cured. In another report, in which the effect of injections of a suspension of verrucous material was recorded, 17% successful results were obtained. In the latter paper, the writer states that the probable effectiveness of the method of treatment used was deprecated to the patients under treatment. In another paper, in which a local injection of 50% urea solution was used on the wart, the observer reported that 91% of his own cases were cured, but that when he induced other physicians to try the same method of treatment, the incidence of cure was some 50%.

It is readily apparent from this review of studies of various methods of treatment of a single skin disease of known etiology, that many associated agents are operative, including time, the site of the lesion, trauma, psychogenic influences, and possible factors as yet unsuspected.

(5) *X-ray therapy of inflammatory diseases affecting the skin.* The discussion of this modality of treatment will be restricted to its use for inflammatory diseases of the skin due to exogenous and endogenous allergens, for the results of scratching, for bacterial infections of acute and chronic nature, and for superficial mycotic infections (excluding ringworm of the scalp).

Since excessive x-ray therapy of any tissue is destructive in its action, and since numerous instances of harmful sequellae on the skin are being seen, it seems advisable to examine our present knowledge of x-ray therapy of acute and chronic inflammatory eruptions of the skin, and subject the tremendous accumulated experience to scrutiny. It is believed that the following principal conclusions may be drawn:

1. There is an enormous and impressive weight of clinical evidence to indicate that following the administration of superficial x-ray therapy to the skin for various inflammatory conditions, many such patients show improvement and some progress to apparent cure. However, some get worse, and the effect of such treatment is often temporary.

2. No planned experiments, to our knowledge, have been carried out with x-ray therapy of inflammatory dermatologic conditions, to determine what proportion of the observed results might be caused by x-ray alone, and what proportion to associated agents such as local therapy, the passage of time, changes in environment, and psychogenic influences.

3. Under conditions in which x-ray therapy for such disease was not available to large numbers of dermatologic patients, e.g., over-seas service in the Armed Forces, one of us (DMP) could detect no significant difference in the numbers of patients who progressed to prolonged dermatologic disability without x-ray therapy, as compared to that noted under conditions of easy availability of such therapy.

4. The precise biologic effect of a few small doses of x-ray given at intervals of 5 to 7 days to the human skin remains to be determined. The mechanisms which have been advanced to explain the action of x-ray on acute inflammatory processes may be regarded as somewhat hypothetical insofar as they furnish an explanation for the involution of a dermatitis or eczema after a few fractional x-ray exposures. These mechanisms, some of which have a sound experimental background (8) include destruction of a proportion of the infiltrating lymphocytes and leucocytes, with "immediate consequence . . . that the antibodies, ferments and other protective substances elaborated in these cells are liberated and made more readily available for defensive purposes", secondary increase in phagocytosis, or an inhibitory action on karyokinesis, or mitotic retardation in the basal cell layer, or formation of antibodies within the tissue, or direct effects upon hyperplastic vascular tissue. Regardless of proof or disproof that one or all of these phenomena occur after the administration of a few small doses of x-ray, it does not necessarily follow that x-ray of and by itself is the principal *cause* of the involution of the inflammatory eruption under treatment.

On the basis of these considerations, it is believed that planned experiments to determine the role of x-ray in *causing* involution of an inflammatory disease of the skin are needed. This seems particularly urgent in the study of the effects of x-ray tubes having very low inherent filtrations and capable of emitting waves of varying types, with potential effects on the skin and other tissues which are as yet incompletely known.

It is hoped that these examples of methods of treatment in which some doubt may exist as to their causal role in the production of a desired clinical effect, constitute sufficient argument for the need of planned clinical investigative experiments in dermatology. It seems particularly advisable that such experiments be carried out adequately in the case of methods of treatment which may have immediate deleterious effects, such as sensitization, or late effects such as may occur after x-ray therapy. The following studies which have been carried out in the Department of Dermatology of the University of Pennsylvania are cited, as examples of effects which may be caused by associated agents, in part to demonstrate that useful information may result therefrom, and in part to indicate that conclusive data from clinical experiments are often difficult to obtain. The first study in a long-term one; the other two are minor studies conducted recently.

Example 1. The treatment of tinea capitis. For the past decade, Livingood, Pillsbury, Newcomer, Kligman, and others in our clinic have been studying the effect of local treatment in this disease, under conditions of adequate facilities for the determination of the causative fungus, sufficient personnel for frequent observation of the patients, and followup facilities sufficient to insure prolonged observation of over 90% of the patients seen. The predominance of patients in whom the causative fungus was M. audouini has permitted study of several hundred patients with this disease. Livingood and Pillsbury (9) found that between 30% and 35% of patients with tinea capitis due to M. audouini progressed to cure with no treatment, or with irregularly applied indifferent treatment. This tendency of some patients to progress toward cure was not related to puberty, or to other determinable factors. Such spontaneous cure required at least

two months, and in many instances the period elapsing until spontaneous improvement was noted was much longer, too long to be of practical value or to satisfy reasonable public health requirements to prevent spread of the disease. It was clear, however, that the factor of *time* was an important associated agent in the cure of M. audouini tinea capitis. This was not in accord with previous concepts of the curability of this type of infection. The question has received continued re-examination in our clinic by Scully et al. (11), Newcomer et al. (12), and by Kligman (13), with complete affirmation that at least one-third of patients with M. audouini infection progress toward spontaneous cure in varying periods of time, and that such a result may be predicted on the basis of slight to severe perifollicular inflammatory response. It is becoming apparent that local

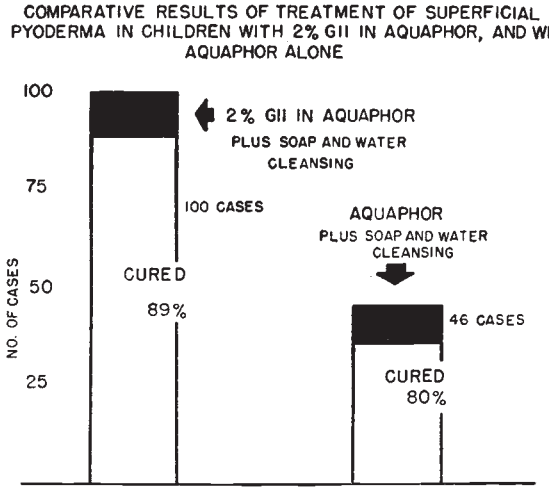

FIG. 2. Comparative results of treatment of superficial pyoderma in children with 2% G11 in Aquaphor, and with Aquaphor alone.

therapeutic agents act not so much through the direct fungicidal action of chemicals contained therein, but rather through their capacity to promote the local immune response.

Example 2. Local antibacterial agents. In the treatment of superficial pyodermas a study of the effectiveness of an ointment containing dihydroxy-hexachloro-diphenyl-methane (hereinafter referred to as G11), in the treatment of superficial pyodermas in children has recently been completed (14). This compound has been shown to have marked bactericidal action *in vitro*, and is effective in reducing the number of bacteria on the surface of the normal human skin (14). Neither of these actions gave assurance, however, that the compound in question would be effective in the treatment of superficial bacterial infections of the skin, and a clinical trial was undertaken.[1] One hundred eight children with various types of superficial pyodermic processes were treated by a routine which included thorough washing of the affected skin with soap and water once daily,

[1] This study was supported by a grant from the Givaudan-Delawanna corporation.

and application of an ointment containing 2% G11 in a hydrophilic ointment base (Aquaphor) twice daily. A "control" series of 46 patients with similar infections were treated by a routine which included washing with soap and water once daily, and application of the hydrophilic ointment *without* G11 twice daily. The objective measurement used was apparent cure of the infection at the end of seven days of treatment. Eighty-nine per cent of the soap and water-G11 treated group were apparently well at that time, while 80% of the soap and water-Aquaphor group were well.

Examination of the data indicated that almost all failures occurred in children in whom the directions as to thorough washing of the skin had not been followed. It seemed justified to conclude that in these patients with superficial bacterial infections, the daily thorough use of soap and water, the application of a hydro-

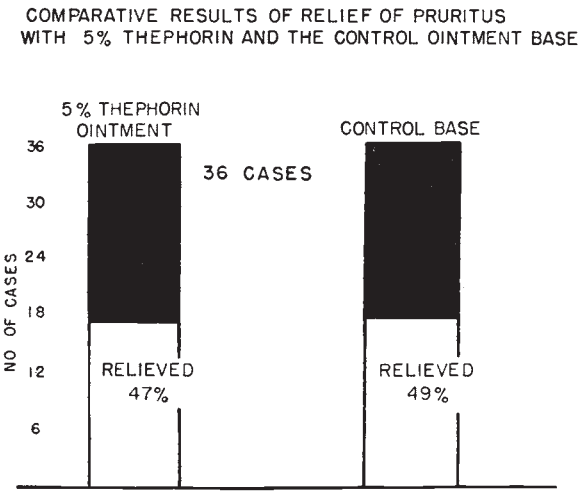

FIG. 3. Comparative results of relief of pruritis with 5% Thephorin and the control ointment base.

philic ointment, and the passage of time variously acted to bring about cure of the disease, and that the use of a hydrophilic ointment containing 2% G11 made a relatively insignificant contribution to this end (15).

Example 3. The local application of anti-histaminics. The introduction of compounds having an anti-histamine effect has been of great value in the treatment of allergic diseases affecting the skin. It is now apparent that the principal usefulness of these compounds when administered by mouth is in the treatment of urticaria, and in some other diseases having an allergic component.

Several studies of the effect of antihistaminic compounds applied locally have been reported (16a–h). In most of them, the interpretation of results have been the relief of itching, a measurement in which each individual patient is the arbiter of improvement. In a series of patients in which the comparative effectiveness of an ointment base, and ointment base plus 2% Benadryl, Perry (17) could detect no significant difference in the control of itching and in objective evidence of

healing of the eruption in a series of patients with various inflammatory diseases of the skin.

Following the report of usefulness of Thephorin in controlling itching by local application to the skin, Baldridge (18) undertook a study in which the comparative effectiveness of ointment base and ointment base plus 5% Thephorin was determined in a series of patients with circumscribed neurodermatitis, atopic dermatitis, pruritus ani and other miscellaneous pruritic eruptions. The ointments used were of similar appearance, and the composition was unknown to the patient. In patients with bilateral eruptions, the effectiveness of the two ointments was compared on the two sides of the body. When this was not possible, the ointments were changed without the knowledge of the patient, and the report of antipruritic effect compared. The same individual observed the patients throughout, and he was aware of the composition of the ointments dispensed, which is undesirable. The comparative results are given in Fig. 3. It will be noted that when an ointment base, either Carbowax or vanishing-type, was used, the over-all relief of itching was estimated at 49%; when similar ointment bases containing 5% Thephorin were used, the incidence of relief of itching was estimated at 47%.

The plan of this experiment was admittedly not ideal. Further study, in which objective improvement of the eruption, determination of the effect of the associated agent of time, and dispensing of the medication and observation of the results by a physician to whom the nature of the ointments was unknown, were contemplated. However, the observation of several patients with convincing evidence of acquired sensitivity to Thephorin rendered the experiment less attractive, and it has been discontinued.

SUMMARY

1. The importance of accurate determination of the role of new methods of dermatologic treatment as the *cause* of subsequent changes in the course of a skin disease is emphasized.

2. The basic requirements of a clinical experiment designed to yield data which will permit conclusions are outlined. Some of the difficulties encountered in planning and pursuing clinical investigative problems in dermatology are listed.

3. Certain examples of standard methods of dermatologic treatment which have received acceptance and are in common use on the basis of uncontrolled clinical observations are cited. It is emphasized that, particularly in methods of treatment capable of producing harm, investigators have a grave responsibility to determine to what extent the clinical result observed was caused by the treatment used, and to what extent by associated agents or through chance.

4. Three examples of clinical studies in which associated agents played an important role in the production of the clinical effect, and in which disregard of these agents would have made a conclusion impossible, are cited.

REFERENCES

1. Albritton, E. C.: Experiment Design and Judgment of Evidence, Edwards Brothers, Inc., Ann Arbor, Mich.

2. Sulzberger, Marion B. and Wolf, J.: Dermatologic Therapy in General Practice, p. 87, Yearbook Publishers, Chicago, 3rd Edition, 1948.
3. Hopkins, J. G.: Measurement of the skin: President's Address, Arch. Derm. & Syph., **59:** 465, 1949.
4. Bloch, B.: Metabolism, endocrine glands, and skin diseases, with special reference to acne vulgaris and xanthoma, Brit. J. Dermat. **43:** 61, 1931.
5. Niles, H. D.: Roentgen rays in the treatment of acne, Arch. Dermat. & Syph. **27:** 89, 1933.
6. Bloch, B.: Über die Heilung der Warzen durch Suggestion, Klin. Wansch. **6:** 2271–2320, 1927.
7. Allington, H. V.: Sulfarsphenamine in treatment of warts, Arch. Dermat. & Syph. **29:** 687, 1934.
8. MacKee, G. M. and Cipollaro, A. C.: X-rays and Radium in Treatment of Diseases of the Skin, 4th Edition, Lea and Febiger, Philadelphia, 1946.
9. Livingood, C. S. and Pillsbury, D. M.: Ringworm of the scalp, J. Invest. Dermat. **4:** 43, 1941.
10. MacKee, G. M., Hermann, F. and Karp, F. L.: A new treatment for anthropophilic tinea tonsurans (M. Audouini), J. Invest. Dermat. **7:** 43, 1946.
11. Scully, J. P., Livingood, C. S. and Pillsbury, D. M.: The local treatment of tinea capitis due to M. Audouini. The importance of inflammatory reaction as an index of curability, J. Invest. Dermat. **10:** 111, 1948.
12. Livingood, C. S., Newcomer, V. D. and Pillsbury, D. M.: The local treatment of tinea capitis due to M. Audouini (to be published).
13. Kligman, A.—unpublished study.
14. Dickey, R. F., Blank, H., Marsh, W., and Hearin, D.—unpublished studies.
15. (a) Traub, E. F., Newhall, C. A. and Fuller, J. R.: The value of a new compound used in soap, to reduce bacterial flora of the human skin, Surg., Gynec. & Obst. **79:** 205, 1944.
    (b) Traub, E. F., Newhall, C. A. and Fuller, J. R.: New cutaneous bacteriocidal agents used in soap, Arch. Dermat. & Syph. **52:** 395, 1945.
    (c) Udinsky, H. J.: Reduction in total skin flora by daily use of a soap containing dihydroxyhexachloro diphenyl methane, J. Med. Soc., New Jersey, **42:** 15, 1945.
    (d) Seastone, C. N.: Observations on the use of G11 in the surgical scrub, Surg., Gynec. & Obst. **84:** 355, 1947.
    (e) Clark, Donald G. C., Lockwood, John S. and Levitt, Elizabeth: Dihydroxy 356, 3′5′6′, Hexachlorodiphenyl methane (G11) as an antiseptic for use in surgical scrubbing, Surgery **22:** 360, 1947.
16. (a) Feinberg, Samuel M. and Bernstein, Theodore B.: Tripelennamine (PBZ) ointment for the relief of itching, J. A. M. A. **134:** 874, July, 1947.
    (b) Sulzberger, Marion B., Baer, R. L. and Levin, H. B.: Local therapy with PBZ hydrochloride, J. Invest. Dermat. **10:** 41, Feb. 1948.
    (c) McGavick, T. H., Schulman, P. and Schutzerr, Elias, H.: Effects of topical applications of diphenhydramine HCl, Arch. Dermat. & Syph. **57:** 308, Mar. 1948.
    (d) Wooldridge, Wilfred L. and Joseph, Herbert L.: Thephorin in the prescription of disseminated neurodermatitis, J. Invest. Dermat. **11:** 93, Aug. 1948.
    (e) Shelmire, Bedford: Experimental topical prescription with thephorin, Postgraduate Medicine **4:** 488, Nov. 1948.
    (f) Laymon, Carl W. and Schmid, J. F.: The topical application of thephorin in pruritic dermatoses, Ann. Allergy, **6:** 638, Nov. 1948.
    (g) Epstein, Stephan and Macaulan, Warren L.: Histadyl cream in the treatment of pruritic dermatoses, J. Invest. Dermat. **12:** 145, 1949.
    (h) Bereston, Eugene S.: Evaluation of histadyl cream, J. Invest. Dermat. **12:** 157, 1949.

17. PERRY, D. J.: The local use of benadryl ointment, J. Invest. Dermat. **9**: 95, 1947.
18. BALDRIDGE, G. D. AND PILLSBURY, D. M.: To be published.

DISCUSSION

DR. MARION B. SULZBERGER: I am sure that all of us are grateful to Dr. Pillsbury for putting this series of basic problems so clearly. First, he has shown that we physicians must never look askance at proper clinical research. Most of us here are physicians, and we must not forget that the result of clinical research is the decisive step; and that, for dermatology, clinical research on the human skin is the acid test, not research on the skin of the laboratory animal, even if he be an anthropoid ape. If pharmacologists and toxicologists had tested penicillin for toxicity in guinea pigs after Fleming had observed its effects on pathogenic mirco-organisms in the test tube, they would most likely have killed all the guinea pigs and we should never have gotten penicillin for human use. I have always been convinced that in all fields of medicine clinical assays on the human being represent the sole reliable and final measure of the value or danger of measures and remedies for human use.

Therefore, for 25 years I have tried to do, and to induce others to do, what Dr. Pillsbury has outlined—sometimes with success and sometimes failure. In evaluating externally applied remedies we have been using the "paired comparison method", thus, as best we could, overcoming the inherent difficulties regarding evaluation of therapeutic measures on the skin, with the many uncontrollable and varying factors which Dr. Pillsbury has mentioned. In many of our studies we have been able to use different remedies comparatively and simultaneously on similar lesions, symmetrically situated in the same individual—and such comparisons have been the basis for much of our group's therapeutic studies. Good examples are our recent clinical pilot studies with the fatty acids, against fungous infections, with results which have been borne out completely by later large scale clinical use.

Among older studies I can mention those of the late Dr. Henry Niles, of the New York Skin and Cancer Unit, who carried out a series of experiments on the "half-face" treatment of acne, one side irradiated with x-ray and the other side with a placebo. Then also, the excellent study of Dr. Allington, who, at my suggestion, carried out a series of treatments of warts by injections of sulfarsphenamine and another by injections of a placebo solution, exactly colored and made to simulate the arsphenamine. Dr. Allington did not know what the material was which he injected in each case. The solutions were prepared and the records kept by a nurse and the doctor did not know which of his patients was getting the colored placebo solution and which the arsphenamine, until the experiment was completed. In both series the results were identical, and mostly good.

I might add, that in consonance with Dr. Pillsbury's ideas, we have at the New York Skin and Cancer Unit a subdivision which has the task of treating all patients who are not treated in other subdivisions by special modalities; antimycotic, immunologic, surgical, x-ray, other physical therapy, etc. All other patients come to a certain unit, which, carries out routine therapy and evalu-

ates therapy. Formerly this Unit was called the "Old Case Room" and neither patients, nor staff members nor students wanted to go there. Now we have changed the name of that division to "Treatment Unit" and under the able guidance of Dr. Frances Pascher it has been engaged in therapeutic assays and standardization of methods for evaluating new and old forms of therapy. In a few years it has thus become one of the most valuable of our teaching and investigative units, whose work is much sought after by students and staff and welcomed by grateful patients.

DR. CONRAD STRITZLER: As Dr. Pillsbury suggested, the evaluation of antipruritics is a hazardous and difficult procedure. In line with Dr. Sulzberger's suggestion, we have been using the method of paired symmetrical comparisons in the evaluation of Thephorin ointment.

A group of patients with symmetrical pruritic lesions were treated by applying the Thephorin ointment to one side, and the placebo control to the other. As the slides indicate, the Thephorin treated side quite regularly showed improvement, whereas the side to which the placebo was applied did not. I feel this approach is a much more objective one than simply asking the patient which preparations gave them more relief.